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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,731	02/19/2004	Kazuhiko Ishikawa	Q79424	4033
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SUGHRUE MION, PLLC 2100 PENNSYLVANIA AVENUE, N.W. SUITE 800 WASHINGTON, DC 20037			CHOWDHURY, IQBAL HOSSAIN	
			ART UNIT	PAPER NUMBER
			1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/780,731	Applicant(s) ISHIKAWA ET AL.	
	Examiner Iqbal Chowdhury, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 5-8, 10 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 9 and 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/10/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-12 are pending.

Applicant's election without traverse of Group I claims 1-4, 9 and 12 in the communication filed on 11/17/2005 is acknowledged. Claims 5-8, 10 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-4, 9 and 12 are at issue and are present for examination.

Claim Objections

Claims 4, 9 and 12 are objected to because of the recitation "sequence set forth in SEQ ID NO: 2" should be "sequence of SEQ ID NO: 2". Appropriate correction is required.

Claims 4, 9 and 12 are objected to because of the recitation "substantial" should be "substantially". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

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In the absence of the hand of man, naturally occurring nucleic acids and /or proteins are considered non-statutory subject matter. *Diamond and Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified protein". For examination purpose the claim is read as such.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4, 9 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4, 9 and 12 are indefinite and vague in the recitation of the "substantially pure" as it is unclear how pure of a polypeptide must be to be encompassed by the phrase "substantially pure".

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 is indefinite in the recitation "at least about 90%" which is ambiguous and confusing. It is unclear whether applicant meant "at least 90%" or "about 90%".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

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art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 4 are directed to a genus of a heat resistant DNA ligases or any DNA ligase having one or more amino acid deletions, substitutions or additions to SEQ ID NO: 2. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches the structure of only a single representative species of such proteins (claims 1 and 4). While claims 2-3 add some additional characteristics to the limitations of the genus of claim 1 i.e. utilization of ATP or ADP and Mg^{2+} , Mn^{2+} , Ca^{2+} or Co as cofactors and specific temperature optima (claim 2) or derived from *Aeropyrum pernix* (claim 3), none of these characteristics alone is sufficient to change the fact that the claims include proteins which are highly variable in both structure as all of these characteristics can be present in proteins of any structure and neither genus recites enough characteristics that a skilled artisan would reasonably expect that any protein having these characteristics would necessarily be highly structurally similar to the disclosed species. Thus for

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all the reasons discussed, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-4 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a heat resistant DNA ligase of SEQ ID NO: 2 from *Aeropyrum pernix* with cofactor dependency to ATP or ADP or Mg^{2+} , Mn^{2+} , Ca^{2+} or Co, does not reasonably provide enablement for any DNA ligase or any DNA ligase having one or more amino acid deletions, substitutions or additions to SEQ ID NO: 2 or any DNA ligase having 90% sequence homology to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1 and 4 are so broad as to encompass any DNA ligase or any DNA ligase has one or more amino acid deletions, substitutions or additions to SEQ ID NO: 2 while claim 9 encompasses any DNA ligase having 90% sequence homology to SEQ ID NO: 2. Claim 2 recites any heat resistant DNA ligase from any source having specific temperature optima and cofactor dependency while claim 3 recites any *Aeropyrum pernix* heat resistant DNA ligase without any identifying characteristics or properties. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA ligase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of

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modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one DNA ligase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass any DNA ligase or any DNA ligase having one or more amino acid deletions, substitutions or additions to SEQ ID NO: 2 or any DNA ligase having 90% sequence homology to SEQ ID NO: 2 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting DNA ligase activity; (B) the general tolerance of DNA ligase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any DNA ligase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

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of the claims broadly including any DNA ligase or any DNA ligase having one or more amino acid deletions, substitutions or additions to SEQ ID NO: 2 or any DNA ligase having 90% sequence homology to SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNA ligase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawarabayasi et al. (PIR Accession No. G72709, "Probable DNA ligase APE1094-Aeropyrum pernix, strain K1, created 8/20/2000). Kawarabayasi et al. disclose the sequence of a protein from Aeropyrum pernix, strain K1, which is 99.9% homologous to SEQ ID NO: 2 of the instant application. Kawarabayasi et al. also disclose that this protein is homologous to DNA ligase and

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the gene was isolated from a hyper thermophilic Crenarchaeon, *Aeropyrum pernix*, which grows optimally at 98°C.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawarabayasi et al. (GenBank Accession No. Q9YD18, "DNA ligase E.C. 6.5.1.1, Polydeoxyribonucleotide synthase [ATP], created 10/16/2000, see IDS). Kawarabayasi et al. disclose the sequence of a protein from *Aeropyrum pernix*, strain K1, which is 97.2% identical to SEQ ID NO: 2 of the instant application. Kawarabayasi et al. also disclose that this protein is a DNA ligase and dependent on ATP and the gene is isolated from a hyper thermophilic Crenarchaeon, *Aeropyrum pernix*, which grows optimally at 98°C and thus a skilled artisan would necessarily expect this protein would be heat resistant to 100°C as recited in claim 1.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Jeon et al. (A novel ADP-dependent DNA ligase from *Aeropyrum pernix* K1, FEBS Lett. 2003 Aug 28; 550 (1-3): 69-73, see IDS). Jeon et al. disclose a gene encoding a putative ATP-dependent DNA ligase from the aerobic hyperthermophilic archaeon *Aeropyrum pernix* K1, cloning the gene of APE1094, which is already known in the art (GenBank Accession No. G72709) that is 99.9% homologous to the instant application and only mismatch is first amino acid, which is methionine instead of valine in the instant application. Jeon et al. also teach biochemical characterization of the resulting recombinant protein encoding a 69-kDa protein similar to other ATP-dependent DNA ligase from the archaea. Jeon et al. further disclose that the DNA ligase in addition to activated by NAD(+) or ATP, also activated and catalyzed strand joining on a singly nicked DNA substrate in the presence of ADP and a divalent cation (Mg(2+), Mn(2+), Ca(2+) and Co(2+)) at high temperature and the optimum temperature and pH for nick-closing activity

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were above 70 degrees C and 7.5, respectively. Jeon et al. furthermore disclose (Table 2) that the activity of the enzyme is not substantially decreased when incubated at 100oC for an hour.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kawarabayasi et al. (GenBank Accession No. AP000060, *Aeropyrum pernix* K1 DNA, complete genome,

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created 6/19/1999, see IDS). Kawarabayasi et al. disclose that APE1094 is encoded by the complement of nucleotides 693527 to 695386 of the GenBank genomic sequence disclosed. Using the genetic code as is well known in the art it would have been obvious to translate the sequence encoding APE1094 to produce a protein having a sequence identical to SEQ ID NO: 2 herein. Note, the sequence of nucleotides 69834-695836 of the genomic sequence is CAC, so the initiation codon is GTG for APE1094. Since GTG encodes a valine, it would be obvious to put valine at the N-terminus. Kawarabayasi et al. further disclose that APE1094 encoding protein is a DNA ligase (predicted) and the gene is isolated from a hyper thermophilic Crenarchaeon, Aeropyrum pernix, strain K1.

Therefore, it would have been obvious to one of ordinary skill in the art to isolate a DNA ligase, which is heat resistant from Aeropyrum pernix as taught by Kawarabayasi et al. and put valine residue at the N-terminus of the amino acid sequence since initiation codon of certain polypeptide use GTG instead of ATG codon.

Conclusion

Status of the claims:

Claims 1-4, 9 and 12 are pending.

Claims 1-4, 9 and 12 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

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